REMARKS/ARGUMENTS

The Office Action

In the above-mentioned Office Action, claims 2, 6, 7, 11, 19, 30, 37 and 38 were rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant believes to be the invention; claims 1-4, 8-13, 16, 18-23, 29, 31-26, 38 and 39 were rejected as being unpatentable over U.S. Patent 6,150,180 (Parce) in view of U.S. Patent 5,856,174 (Lipshutz); claims 5, 6, 14, 15, 28 and 30 were rejected as being unpatentable over Parce in view of Lipshutz as applied to claims 1 and 3, and further in view of U.S. Patent 6,007,690 (Nelson); claims 5, 7 and 30 were rejected as being unpatentable over Parce in view of Lipshutz as applied to claims 1 and 3, and further in view of Heegaard, et al., *Journal of Chromatography B,* Sept. 1988, Vol. 715, pp. 29-54 (Heegaard); claim 17 was rejected as being unpatentable over Parce in view of Lipshutz as applied to claim 1, and further in view of U.S. Patent 4,816,123 (Ogan); claims 24 and 25 were rejected as being unpatentable over Parce in view of Lipshutz as applied to claim 1, and further in view of U.S. Patent 5,324,401 (Yeung); claim 26 was rejected as being unpatentable over Parce in view of Lipshutz as applied to claim 1, and further in view of U.S. Publication No. 2003/0134416 (Yamanishi); claim 27 was rejected as being unpatentable over Parce in view of Lipshutz as applied to claim 1, and further in view of U.S. Publication No. 2002/0115201 (Barenburg); claim 36 was rejected as being unpatentable over Parce in view of Lipshutz as applied to claims 1, 35 and 36, and further in view of U.S. Patent 5,246,577 (Fuchs); claims 1-9, 12, 13, 16, 20-23 and 33 were provisionally rejected under the judicially-created doctrine of obviousness-type double-patenting as being unpatentable over claims 1-28 of U.S. Patent 6,406,604 in view of Lipshutz; and claims 1, 2 and 33 were provisionally rejected under the judicially-created doctrine of obviousness-type double-patenting as being unpatentable over claims 33 and 34 of copending U.S. Patent Application No. 10/821,328.

The Amendments

Claims 1-39 are cancelled without prejudice or disclaimer. New claims 322-429 are added.

The title was amended to better correspond to the invention of the new claims.

In the specification, paragraphs [0095], [0099], [0101], [0106]-[0109], [0111], [0119]-[0120], [0123]-[0125], [0127], [0103]-[0135], [0138], [0140]-[0144], [0146]-[0150], [0156], [0162], [0163], [0165]-[0166], [0168], [0170]-[0172], [0174], [0178], [0180], [0182], [0186]-[0189] were amended as required by the Examiner to correct informalities.

Regarding the Examiner's refusal to consider the reference WO 97/11362, Applicant submits herewith a Supplemental Information Disclosure Statement with the equivalent Japanese publication JP 09-080021 and a computer translation.

The New Claims

In the above-mentioned Office Action, dependent claim 29 was rejected over Parce in view of Lipshutz. Dependent claim 29 includes the "staggered" configuration feature of this invention. In particular, the Office Action states that "[w]ith respect to claim 29, Parce et al. teaches the apparatus of claim 1, where two adjacent transport passages are staggered at each of the analyte concentrators (FIG. 5 and FIG. 6A). All of the pending claims have been cancelled and a new set of claims – claims 322-429 – have been added. The new claims include four independent claims, each of which includes in one form or another the "staggered configuration" feature.

The "Staggered Configuration" Feature of the Invention

The staggered configuration for the intersection of the transport passage with a separation passage is shown, for example, in FIG. 11b of the present application. This can be contrasted with the non-staggered passage as shown in FIG. 11a. The staggered configuration is also shown in FIGS. 18, 19, 22, 28a and 28b. Paragraph [0149] discusses the staggered construction as illustrated in FIGS. 28a and 28b. The analyte concentrator is designed in a staggered configuration in the above-mentioned FIGS. 18, 19, 22, 28a and 28b, for example, to allow the passage of large volumes of

fluids (e.g., microliters and milliliters). The staggered configuration has a large surface area to permit the maximum capturing and concentration detection of any type of analyte, such as small molecular weight substances and biomolecules.

Paragraph [0107] discusses how the transport passage can be staggered from one separation passage to another to form a staggered concentrated area. The area is elongated which advantageously allows additional matrix-like assemblies to be incorporated therein to attach a desired analyte from the sample solution. In addition, the sample solution advantageously takes additional time to pass through the elongated concentration area (as opposed to a straight, non-staggered area), which thereby provides the matrix-like assembly additional time to bind to the desired analyte from the sample solution. (The concentration area may be surrounded by frits or porous end plates to retain the matrix-like assembly within the concentration area.)

Paragraph [0113] mentions that an elongated concentration area, as illustrated in FIG. 11b, may be provided to expose the sample solution to the matrix-like assembly for a longer period of time and to a longer surface area to capture larger amounts of desired analyte(s).

Paragraph [0133] discloses how the valves can be operated so that the sample solution passes through the staggered area as desired, across the transport passage without contaminating the separation passages from the large and diverse number of substances present in the sample solution under study.

The present invention can thus include this staggered configuration to immobilize affinity ligands, to enhance the surface area of binding, to create a microenvironment to facilitate optimization of binding utilizing optimal temperatures and micromixing, to even be able to derivatize components at the analyte concentrator micro-reactor or using a second concentrator. Further, the analyte concentrator in the staggered configuration not only is a concentrator, but can also be a micro-reactor allowing multiple enzymatic/chemical/biochemical/cellular/and subcellular reactions to occur. The staggered configuration of the present invention allows cellular and subcellular organelles to be trapped and endogenous metabolites to be formed or induced metabolites to a particular drug.

In other words, "the staggered configuration" of the analyte concentrator-microreactor connects the transport tube to several separation passages. A larger capturing surface area is provided by the staggered configuration when compared to the linear configurations or the cruciform configurations such as shown in FIG. 11a. Thereby, the amount of immobilized affinity ligand is the largest without producing back-pressure when introducing samples into the transport passage. The inner diameter of the transport passage can be greater than that of the separation passages. The sample can be injected by a "side" connection to the separation passages, rather than from inlet to outlet in a straight configuration of the separation passage. The concentrated samples pass via the separation passages to the detector system to identify and characterize the analytes of interest delivered thereto by electrophoresis migration.

A larger amount of fluid is transported through the transport passage in a staggered configuration embodiment without affecting the integrity of the separation passages. Specifically, nanoliter volumes can be introduced into the transport passage, or microliter volumes, or milliliters, or maybe even liter volumes of samples containing from one substance to many millions of compounds present in simple or complex fluids or tissue or cell extracts can be applied in the transport passage of an electrophoresis apparatus of the present invention.

The multi-dimensional geometry of the analyte-concentrator of this invention permits dozens or hundreds of affinity ligands to be immobilized, in order to capture hundreds or even thousands of substances present at various concentrations in a diversity of fluids. This configuration thus allows a "high-throughput" method to assay large numbers of substances in a short period of time. Furthermore, the configuration permits the immobilization of all kinds of affinity ligands, allowing many kinds of interactions in a true multi-dimensional system.

There is basically no possibility of false positive results when compared to conventional immunoassays such as ELISA (Enzyme-Linked Immunosorbent Assay), because even though it may capture a similar substance, it provides a second method (the separation passages) separating the components by electricity (electro-osmotic flow), pressure, vacuum, or a combination of them. The high-resolving power of

capillary electrophoresis can differentiate the true related antigen or hapten to the immobilized antibody from the non-related compounds.

Further, an electrophoresis apparatus of the present invention can have valving surrounding the staggered configurations to control the flow of fluid from the transport passage through the staggered configurations and into the associated separation passages. The valves control the flow of fluid, and also provide a micro-environment in which the temperature, time, vibration, etc. can be controlled to optimize to the conditions the binding between a target analyte and an immobilized affinity ligand (e.g., antigen/antibody, sugar/lectin, enzyme/substrate, etc.).

The valves permit the full control of the direction of the flow, forcing the sample and cleaning buffers to go from the inlet of the capillary (submerged in a sample container or a cleaning buffer container) to the outlet of the capillary (submerged in a waste container). This feature provides a complete protection of the separation capillary (or separation channel). In other words, the sample to be analyzed and the cleaning buffers will never contact the separation capillary. Thus, the separation capillary can be easily regenerated after each use since there will be only a selected number of analytes to be separated, permitting the re-use of the separation capillary a few hundred times.

FIG. 5 of Parce refers to the description of a "sample shunting or extraction." The samples or test compounds (504) are introduced to the channel (512) of the chip via a capillary pipettor. The sample continues traveling through the "sample channel" as discrete plugs embraced by two guard bands ("sample plugs"). The "sample plugs" are separated from each other by "spacer solution plugs" (502), until they reach the "reaction channel" (510). Once in the "reaction channel" the test compound reacts with the "receptor" in the "first incubation zone" (510a) and then with a fluorescence ligand in the "second incubation zone" (510b).

The speed and direction of the "sample plugs" (containing receptor, fluorescent ligand, and test compound) in the "reaction channel" (510) depend on the potential applied in the different reservoirs (514, 516, 518, inlet of 512, 520, and 522). Within the "separation channel" (524), the "sample plug" may be exposed to different conditions

than those of the "reaction channel." Samples are "shunted" into the "separation channel" to remove the spacers and allow the separation of the various sample components outside the confines of the original sample plug. The volumes introduced into the channel can be in the picoliters range and may be femtoliters. Each injected sample contains not only the test compound, but also all other compounds present in the sample. Therefore, the only possibility of assessing the effect of the test compound on the enzyme-substrate or receptor-ligand is to measure the decrease or increase of the fluorescence intensity of the complex. The only purpose of this assay is for gross screening of test compound reactivity. There is no concentration effect whatsoever, and it is prone to questionable information of the data, due to the significant low concentration that the test compound may be present in the sample. Furthermore, there is no possibility for the use of UV detection or connection to a mass spectrometry in Parce.

This concept of "shunting or extraction" to the "separation channel" for true separation is a different concept than and does not disclose or suggest the "staggered configuration" of the present invention. FIG. 5 is almost identical to FIGS. 1 and 2, with the exception of the shunting process. Every action is in motion; therefore, it belongs to the type of "Free-Solution Affinity Capillary Electrophoresis". There is no immobilization for "concentration" purposes ("Immobilized Affinity-Ligand Capillary Electrophoresis"). The "sample plugs" are picoliter volumes and perhaps femtoliter volumes. In the subject invention they can be micoliter, milliliter, or even liter volumes, if necessary. Also, the present invention can permit cleaning all unwanted materials by the cleaning buffer, leaving attached to the immobilized ligand only the "target analyte" of interest. The present invention is not limited to fluorescent or chromogenic detection systems, but all detection systems individually or in combination can be used.

In the present invention, both preconcentration on-line and microreaction on-line can be carried out. In Parce, there is no concentration. The amplification or diminishing of sensitivity is only due to the fluorogenic or chromogenic activity. The "staggered configuration" of this invention allows for the immobilization of a panel of "affinity ligands" to capture, enrich, and clean multiple "target analytes". The present invention

can be regenerated and re-used multiple times, while Parce's is disposable; one use of the chip at the time, and not in favor of pumps and/or valves.

Interview Summary

The undersigned counsel and Dr. Guzman thank Examiner Jung and her supervisor Mr. Lee for the courtesies extended to them during their personal interview of February 21, 2006. During that interview the examiners agreed that the four new independent claims were patentable over Parce and that the claims were not subject to a restriction/election requirement.

Concluding Remarks

Accordingly, it is respectfully contended that all of the claims now pending are in condition for allowance. Issuance of the Notice of Allowance at an early date is thus in order.

If there are any remaining issues, the Examiner is encouraged to telephone the below-signed counsel for Applicant at (310) 785-5384 to seek to resolve them.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 10-0440. Should such additional fees be associated with an extension of time, Applicant respectfully requests that this paper be considered a petition therefor.

Respectfully submitted,

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